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EDITORIAL

MEDICAL ETHICS AND QUACKS.

The unwritten laws of Medicine cost the people millions of dollars annually! How? Because of the sale of patent medicines, because of the advertising necessary to sell these medicines and because of the delay which results from their use in receiving decent medical attention. Why? Because individually the doctor is frowned upon if he decries their sale and use, and collectively the medical profession do little or nothing, that is apparent at any rate, to combat this evil. The public are skinned, fleeced of gold dollars, silver coins and health because of the deluge of vitamins, irradiations, preventatives, cures and universal panaceas for all ails, that crowd upon the shelves of our drug stores. Truly the people are guinea-pigs! We know it and are—silent.

We agree that the individual doctor should not take it upon himself to become involved in a newspaper war with the manufacturers and sellers of these drugs, but we do feel that, this privilege being denied, the medical profession as a whole, through the voice of its association, should openly and vigorously conduct a campaign against this nefarious exploitation of the public. That such action would be greeted

with success is shown by the popular opinion that prevails upon the deleterious action of aspirin on the heart. This popular belief was produced by only one or two articles in one of our popular magazines some years ago.

Therefore, in those cases where the doctor is prevented from voicing his opinion publicly, it is up to our association to serve the profession and the public alike by voicing opinions on such matters as pertain to the good of the people.

* * *

And while this public spirited mood is upon us, mention might be made of the recent investment of some power to control the athletic activities in the Province under the Minister of Health. This seems to be a very sound step, for though Public Health is not the only line of attack, yet it is felt that much could be done in this connection for the physical well-being of the people. Physical education is something which our educational system sadly neglects and seemingly underestimates. It should be as integral a part of our studies as geometry, history, literature, etc., instead of being relegated to a very puerile hour which is shirked at every possible opportunity.

By this move the Department of Public Health have begun to place themselves in a position to bring about such changes in our curriculum. And to those who take a far-sighted view of the situation, the day can be visualized when Public Health will be able to dictate to the Employed on behalf of the Employee, in cases where health is being interfered with because of lack of even hypocritical charity.

We have sadly missed our chance during the depression in not educating our unemployed physically, as well as gastronomically. Surely with men sound of body and mind, work would be something to be sought after above all else. We admit freely that this is not a solution to the present great difficulties that the State is labouring under at the moment, but the plea is made here that we have long aided the mind, but let the body carry on in its own sweet way, which is not necessarily the best way. It is therefore to the Public Health branch of Medicine that we look for help in order to live according to the ordinary laws of health and decency.

* * *

A glance at the titles of the articles appearing in the first part of this issue will show the reader that quite a symposium on Bacterial activity is presented, the discussion ranging from the general to the particular. It will also be noted that this is composed of undergraduate work entirely, but of a very high calibre.

In viewing our conception of bacteria and their activity, it will be seen that we have advanced, perhaps without realizing it, a long way in this field from the time of Pasteur. We realize that the evidence of such activity, clinically, is a change in the dynamic bacterial activity, and our evidence taken at any one moment is just a cross-section of the observable history of these organisms. That is, the conception of a time element, a fourth dimension if you like, must be taken into account.

Then too, emphasis is gradually moving from the bacteria to the tissues upon which they thrive. We have been accustomed to thinking that bacteria damage the tissues and hence they localize in that place. May not the converse view be tenable, that bacteria localize in one area because some change has taken place in that tissue, which makes it less resistant to their activity? And with the broadening of our conception of allergy and the factors that go to produce that state, we are led to consider not only the local reactions to the presence of bacteria, but the reaction of the organism as a whole.

Hence the field of Bacteriology, in order to gain a new impetus and new life, must investigate not only the bacteria and their properties but the tissues on which they live, the time which they live there, and the total response of the organism to their presence.

RESISTANCE TO BACTERIAL ACTION

By JOHN DAVID ROGER, '39.

The body protects itself in several ways against the action of bacteria which penetrate the tissues. In the early stages of the study of resistance, the French school considered this resistance to be due entirely to "phagocytosis" of the bacteria, i.e., their ingestion and digestion by certain cells of the body, the "phagocytes." The German school maintained that resistance was due to certain substances present in the plasma of the blood, the "antibodies." More recently, the conclusion has been reached that neither theory alone explains the method of protection entirely. It is now believed that resistance is achieved by the combined action of phagocytes and antibodies, along with a more recently discovered agent, the "bacteriophage." It is probable that phagocytosis is the most active agent, but it will not occur without the cooperation of the antibodies. On the other hand, these can act independently of the phagocytes. To what extent the bacteriophage takes part in resistance, is not yet definitely known.

Phagocytosis.

The Phagocytes. There are three types of phagocytic cells in the body. The neutrophile polymorphonuclear leucocytes or "microphages" are probably the most important. The monocytes or mononuclear leucocytes are somewhat less active in phagocytosis. Certain large endothelial cells lining the serous cavities, the blood vessels and the lymphatics are also capable of ingesting foreign material, but not to nearly so great an extent as are the leucocytes. These endothelial cells, with the monocytes, make up the group termed the "macrophages."

To a certain extent, the variety of the bacteria responsible for the infection determines the variety of phagocyte which will be most active in their phagocytosis. In the destruction of the bacteria of most acute infectious diseases, the microphages play the most important part; the macrophages acting largely as scavengers. Other invaders, such as the bacteria of chronic diseases, pathogenic yeasts and many animal parasites are opposed chiefly by the macrophages.

Locomotion and Ingestion. All the phagocytic cells are able, owing to their power of contraction and expansion, to project portions of their photoplasm in the form of pseudopodia. These flow around and engulf particles of foreign material that may be harmful to the tissues. The microphages and monocytes, termed "wandering phagocytes," also possess the power of locomotion. They travel by projecting the pseudopodia on one side and the remainder of the cell protoplasm flows along the pseudopodia; the process is thus continuous. Occasionally the phagocytes propel themselves by projecting several such pseudopodia which stretch out several times the diameter of the cell in the form of flagella. The phagocytes are carried from one part of the body to another by the blood stream, and, on leaving it, progress through the tissues by means of the pseudopodia or flagella.

Chemotaxis. Invasion of the body by bacteria is followed by a prompt response on the part of the wandering phagocytic cells. A large number of them quickly congregate at the point of infection. This phenomenon, "positive chemotaxis," indicates that some means of communication must exist between the point of infection and the cells in the circulating blood. There is no direct connection by the nervous system or other structural methods, so the only possible explanation is that communication is through the fluids of the body.

The methods by which chemotaxis works are not clearly understood, beyond the fact that they are associated with changes in the chemical composition of the blood. The most generally accepted theory attributes chemotaxis to surface tension phenomena. It suggests that in positive chemotaxis, the chemotactic substances, diffusing through the blood to the leucocyte, lowers its surface tension on the side at which they are most concentrated. Pseudopodia are projected on this side and in consequence the leucocyte moves in this direction. Conversely, in "negative chemotaxis" in which the leucocytes retreat from the point of infection, the nature of the chemotactic substances secreted by the bacteria is probably such as to increase the surface tension on one side. This would cause the protrusion of pseudopodia on the opposite side and movement away from the site of infection.

Ingestion. The ingestion of bacterial cells by the phagocytes is considered to be a further expression of positive chemotaxis. The pseudopodia sent out, surround the bacterial cell and the cell is taken into the cytoplasm of the phagocyte. A single phagocyte is capable of ingesting a very large number of bacteria, and may seem to be almost completely filled with them, except for the nucleus. Experiments outside the body have shown that the phagocytes will only ingest bacteria to a very limited extent, unless the bacteria are first acted upon by the serum. The substances in the serum necessary for the ingestion of the bacteria are termed "opsonins." It is thought that their action makes the surfaces of the bacterial cells more adhesive to the protoplasm of the phagocytes, thus facilitating ingestion.

Digestion. After the bacteria have remained for some time in the cytoplasm of the phagocytes, vacuoles similar to the digestive vacuoles of the amoeba may be seen to form around them. As the digestive ferments of the phagocytes act upon the bacteria, they begin to disintegrate, lose their form and become enlarged, granular and vacuolated and finally no longer distinguishable. On the other hand, if, as sometimes happens, the ingestion of the bacteria brings about the death of the phagocyte, the digestive vacuoles do not form and the phagcyte itself disintegrates.

Resistance to Phagocytosis. Not all micro-organisms are equally susceptible to phagocytosis. Some are able to resist ingestion more energetically than others by agencies not fully understood. The bacteria of chronic diseases exhibit considerable resistance to phagocytic digestion and may be ingested without being harmed. It is because they possess special qualities which protect them against the phagocytes, that certain bacteria manifest extreme virulence. Some escape phagocytosis by secreting "aggressins," substances which dissolve the leucocytes and neutralize the opsonins. The ease and rapidity with which others move helps them to escape. The negative chemotaxis produced by some bacteria prevents the phagocytes from attacking them.

Degrees of Phagocytic Activity. Under certain conditions, phagocytosis is much more energetic. Animals of a type naturally fairly resistant to a certain disease show much more active phagocytosis of the bacteria of that disease than do animals of a type naturally more susceptible. In the case of an individual immunized against the attack of a certain micro-organism, the phagocytic activity against that organism is much more energetic than in the case of a non-immunized individual. It is also true that the more virulent the invading micro-organism, the less active is the phagocytosis.

Antibodies.

General.—If "antigens," viz., bacteria, bacterial extracts, or in fact practically any protein substances, are injected into the body, the blood will take on certain properties considered to be due to the appearance in it of

substances termed "antibodies." The antibodies develop as a reaction against the presence of the antigens. It is thought that they are formed in the reticulo-endothelial system of the body, but this has not been definitely proved. For a few days after the injection of the antigens no antibody properties appear in the blood; then they appear suddenly in considerable strength, increase for a few days, and gradually diminish again.

The antibodies have never been isolated. They are known solely by the phenomena resulting from their action. They have been divided into several classes, according to these phenomena. Of these classes, those important in the defence of the body against bacterial action are: the "agglutinins," "precipitins," "bacteriolysins," "opsonins," and "antitoxins."

It is possible that, as some writers contend, there is only one type of antibody responsible for all the reactions attributed to these different classes, the different phenomena depending on the condition and environment of the bacteria. However, this does not seem to be the general belief.

The function of the antibodies appears to be to protect the body from the harmful effects of the presence in it of bacterial organisms. To do this, the antibodies must unite with their respective antigens. The agglutinins, bacteriolysins and opsonins unite with whole bacteria. The antitoxins and preciptins unite with products excreted by the bacteria and with products of bacterial disintegration, respectively.

There have been several theories advanced as to the way in which the antibodies and antigens unite. One suggests that the reaction is like that between a strong acid and a strong base. This theory has been shown to be untenable by the discovery that in neutral toxin-antitoxin mixtures, there are always free toxin and antitoxin present, as well as the two combined. One theory which takes this into account compares the reaction with that of a weak acid and a weak base. These do not completely dissociate, and in the resulting mixture, free acid and base are present, as well as the salt. The most generally accepted theory is that the reaction of antigen and antibody is not a chemical one, but is similar to the colloidal adsorption of colouring matter in some dyeing processes. It is thought that the molecule of the antigen absorbs the antibody and so becomes neutralized.

Opsonins. The opsonins make up one of the classes of antibodies. They must be present in the blood for effective phagocytosis to take place. The phagocytes will not attack bacteria to any useful extent, unless opsonin is present, to act on the bacteria and prepare them for ingestion as already described.

The opsonins present in normal and immune sera do not seem to have exactly the same properties. In this they are different from the other antibodies, which seem to be of the same nature in normal and immune sera; merely being present in greater quantity in the latter. When normal serum is heated to 60°C, its opsonic action is quickly destroyed, while immune serum may be heated for a considerable time without any apparent change in its opsonic action being produced. Both normal and immune opsonins are specific for different antigens; i.e., an opsonin formed as the result of the entrance into the body of bacteria of one type will have no effect on bacteria of an altogether different type.

Normal opsonins act in many ways like the "complement" of the blood, which is a ferment-like substance normally present in the blood and easily destroyed by heating. This has suggested that the two substances are identical; more recently this fact has been taken to indicate that the complement is merely a necessary agent in normal opsonic action. The most generally accepted idea is that the action of normal opsonins depends on a substance easily destroyed by heat (probably the complement), cooperating

with a substance less easily affected by heat, the opsonin itself.

In the case of immune opsonins, the complement is not necessary for the action, although it may increase it.

Bacteriolysins. When bacteria gain access to the blood of an immune animal, they lose their motility, become swollen and granular, and finally dissolve. This phenomenon also occurs in the blood of animals not immune to those bacteria, but not to nearly so great an extent. It is termed "bacteriolysis", and is considered to be due to the action of one of the classes of antibodies, the "bacteriolysins".

In some instances the bacteria appear to be merely killed without being dissolved, and for a time it was thought that this was due to another type of antibody, "bactericidin". More recently the conclusion has been reached that this is the result of differences in the bacteria; some being more resistant to the lytic action than others, and so, although killed, are not dissolved.

Bacteriolysins appear to be specific for the antigens which cause their formation. It is thought that in lysis, the bacteriolysin unites with the bacteria, and that this makes them susceptible to the attack of the complement. Then, when the complement unites with them, lysis results. With the more resistant bacteria the bactericidal effect results.

Agglutinins. When serum from the blood of a person immune to the attack of a certain type of bacteria is added to a uniform suspension (in vitro) of those bacteria, they rapidly lose their motility if motile, and group together in small clumps. This phenomenon is considered to be due to the action of the "agglutinins" of the blood.

The bacteria are entirely passive in the agglutination and their motility has no relation to it. At first, some of the investigators thought that the reaction was concerned with some change in the flagella of bacteria, but it has since been proved that this is not the case. It is now known that non-motile as well as motile bacteria will undergo agglutination, and that in the case of flagellate organisms, there is no perceptable change in the appearance or arrangement of the flagella. It is thought that agglutination occurs in two stages. The agglutinin first combines with its antigen in the suspended bacteria. The agglutinin and suspended bacteria are both colloidal in nature, and their union, produces a complex which is then caused to clump by the presence of electrolytes.

Agglutinins are specific for the antigens which cause their formation. This fact is of considerable use in the diagnosis of certain diseases, notably typhoid fever. A little of the serum of the patient is diluted considerably and added to a uniform suspension of bacteria of the suspected disease. The occurrence of agglutination indicates that he has the disease. The dilution of the serum is necessary because, while the agglutinins are most active for the bacteria which cause their formation, they are also active, though to a much less extent, for bacteria of related types.

Precipitins. The precipitins are considered to be another class of antibody. Their action is very similar to that of the agglutinins, but is regarded as a clumping of protein molecules rather than of whole cells. It produces a light, flocculent precipitate.

It is thought that a specific part of the antigen, "precipitinogen," causes the formation of the precipitin, and unites with it in the precipitation reaction. The reaction is produced only when the two reacting substances are present in suitable proportion.

Precipitins are specific, and are used in conjunction with agglutinins in identifying bacteria.

Antitoxins. The action of the antitoxins is probably more important than that of any of the other antibodies in protecting the body from the harmful results of the attacks of micro-organisms. Although the invasion of the body by bacteria may result in destruction of tissue, most bacteria seem to inflict their greatest harm by the liberation of "toxins". These appear

to enter into some harmful form of combination with susceptible cells of the body. It is thought that the antitoxins unite with the toxins before the latter can unite with the cells, and thus prevent the harmful combination.

There have been several other theories advanced concerning the way in which antitoxin prevents the harmful action of toxin. One of the earliest, suggested that the toxin was directly injured or destroyed by the antitoxin in the blood. Another maintained that the antitoxin acted in some way upon the cells of the body to protect the cells from the attack of the toxin.

Both these theories have since been disproved, and it is now practically certain that the reaction is an adsorption of the antitoxin by the toxin molecules. This adsorption makes the toxin inactive but does not actually harm it. If the antitoxin is destroyed, e.g. by freezing, the toxin will become active again.

The Bacteriophage.

A phenomenon which it is thought may be important in the resistance of the body to bacterial action is a dissolving of the bacterial cells. This action is different from that produced by the bacteriolysins already described. This is shown by the fact that it may be transmitted to cultures, not previously affected by adding to them a few drops of the bacteria-free filtrate from a culture in which the lytic action has occurred. Again, if a drop of the filtrate from one of these cultures is added to another culture, lysis takes place in it, and this transmission may be continued any number of times.

The cause of this transmissible lysis is called, "bacteriophage," and there are several theories as to its nature. The fact that a very slight trace of the filtrate from an affected culture can reproduce the action in large quantities of a new culture; and that a small amount of the filtrate from this can then transmit the action again (and so on, indefinitely) has led many investigators to think of the bacteriophage as a living, self-propagating, ultramicroscopic parasite of the bacteria. Other workers suppose that the bacteriophage is an enzyme or proenzyme of the bacterium, acting as a catalyst in producing the destruction of the cell. Some investigators hold that it is a growth-producing hormone of the bacterial cell and that this hormone has become changed in some way which makes it harmful to the bacterium. Still other investigators have advanced the theory that the transmissible agents are hereditary factors or genes which determine self-destruction; and which, on liberation by the disintegration of the bacterial cells, penetrate normal cells and confer on them the suicidal character.

The bacteriophage may usually be obtained from the faeces of animals and man, and sometimes occurs in the blood, especially during recovery from infectious diseases. Besides the destruction of bacteria by dissolving them, it appears to aid the body in its fight against bacteria by an opsonic action which makes the bacteria more easily ingested by the phagocytes. It is thought that it may also lessen the virulence of the bacteria by causing a structural change in the bacterial cells, but there is no evidence that this occurs in resistance to bacterial action.

The study of the methods by which the body resists bacterial action has shown ways in which the body may be helped in its struggle. Vaccination and innoculation are practised extensively to aid in this struggle. Experiments with the oral administration of material containing the bacteriophage seem to show that this is also of assistance in some diseases although as yet this has not been definitely proved.

FOCAL INFECTION IN INFANTS AND CHILDREN

By J. W. MAGLADERY, '35.

Focal infection has changed, with ever-increasing evidence, from a theory to a principle of infection, and at the same time, a goodly number of patients that are seen in the wards who are suffering from a chronic disease, of almost any type, give a history of earlier attempts at removal of foci of infection. Whilst definite improvement has resulted in many cases, only too often it is felt (much too frequently by the patient) that the removal of the focus has resulted in little or no improvement. Why should so many patients fail to respond to this rational method of treatment? This question may be answered by two very good reasons, viz. that there is:—(a) an inadequate appreciation of what a focus of infection means and of the manner in which it might produce far-reaching effects; (b) an attempt too late, perhaps 50 years too late, at the removal of a cause which has long since produced its damage. With these in mind, it is the purpose of this paper to present a sketchy review of the principles of focal infection and to urge their application clinically at a time when definite results may be obtained, that is, in infancy and early childhood.

It is almost self-evident that practically all bacterial, protozoal, or virus infections must have a portal of entry with a primary focus from which the distribution follows. This is too broad a conception, however, and focal infection has come to have a special meaning. It might be defined as a chronic, usually low-grade, infection that develops insidiously and progresses slowly, producing symptoms of local and systemic disease. It is a common primary cause of chronic ill-health, but also probably plays a very important part in augmenting, maintaining, or aggravating disease originally due to other causes. The focus (or foci) may be primary or secondary, and the dissemination of infective or toxic materials may be constant in character or varying intermittently with many factors.

It is necessary, therefore, to consider in each patient what criteria are suggested before incriminating any one focus as the contributory factor to the infection and the condition found in the patient. First, the foci must be found. These may, but more frequently don't, show symptoms of definite local activity, so painstaking effort must be put forth to find all those that may be responsible for the condition. The foci found, it is necessary to balance the evidence for and against their importance in the given circumstances. The local condition may offer a clue; a history of previous disease in the organ or tissue may be of value; the finding of bacteria may sometimes be useful; the evidence of a blood stream infection is of great help diagnostically.

It is felt that, due to the great lack of controlled clinical experiments and the wide field involved in the results of focal infections, it would be more profitable to delve into the realms of bacteriology, proven and theoretical, and to attempt to link our theories with a very few clinical entities which are of interest to the paediatrician in particular.

The bacteriology of focal infection seems to be largely that of the streptococci, but beyond that it is difficult to go. Some believe that various members of the group produce distinctly different results in the body. Others are convinced that the streptococcus viridans is only a stage in the process of the reaction of the hemolytic streptococcus to the defence mechanism of the body, producing different results.

It is almost universally agreed that all bacteria respond to the reactions of the animal body in the infections, and become altered in various ways. Rosenow's theory of elective localization has its supporters and antagonists. In other words, the literature is a maze of contradictory beliefs and experimental results. Apparently we must evolve an attitude which will accept various cultural types of organism as taking part. It must not, however, be thought that focal infection is in any way confined to the streptococcus group. Pneumococci, staphylococci, gonococci and many other bacteria invade the body from a primary focus of infection; the streptococci have received such stress due to their higher invasive power and more frequent occurrence.

Let us look at any focus of infection, for instance, an infected tonsil, and consider its relation to the rest of the body. Here is a local area, the site of many organisms of a relatively low virulence, and temporarily walled off from the rest of the host. There are a variety of ways in which it can produce a remote effect. Let us consider them individually and the way they may act in relation to defence mechanisms of the body.

Bacteria may enter the blood stream (or the lymphatics, for that matter) as whole bacteria. Here they are met by the different mobile forces of resistance; the phagocytes, opsonins, agglutinins, bacteriophage, etc. and usually destroyed or rendered available for removal by the reticulo-endothelial system. Filterable viruses or pathogenic exotoxins may be cast intermittently or continuously into the blood stream. Here we have very little idea of the type of resistance put up by the circulating blood, but it seems probable that certain organs bear the brunt of the attack. Finally, small portions of the bacteria or non-specific toxins (possibly of a protein nature) may be repeatedly given off to the general circulation. These, too, are normally handled by the antibodies, whatever they may be. This last suggestion must, of necessity, lead us to a consideration of those closely allied states, immunity and sensitization. These are terms which we all glibly use, often with little idea as to their possible meanings or differences. The following conception makes the problem seem a little more real.

Let us introduce any foreign protein into the blood stream—let it be egg white, foreign serum, cultures of bacteria, or emanations from a focus in the body. This deluge of a foreign material, sufficiently like the proteins of the blood stream that it is not excreted by the lungs, kidney or sweat glands, is met by the various ill-defined forces of the blood. Union of the two types of protein material (i.e. from the blood stream and the invader) produce what we call antibodies. If the host originally had enough of the protective protein material circulating in its blood stream to link up with all the invading substances successfully, and change it completely into antibodies, the onslaught has been met without effect on the different tissue cells of the body, and a resistance of antibodies has been prepared for future use. This is what we term *immunity*. If, on the other hand, the circulating blood is permanently, or perhaps only temporarily, unable to muster enough of the resisting elements at the time of invasion, some of the foreign protein will be left over, unchanged to antibody, and carried to all parts of the individual, prepared to carry out some change in the tissue cells. The changes differ with tissues and locations but are usually such, that a second administration of protein causes a marked reaction, usually of an exudative nature, and affecting the whole body. This is *sensitization*, and possibly the basis of the symptoms of many of our systemic diseases. The degree of immunity or sensitization may vary and may play a small or great part in the defence of the body. General immunity developed to the protein of a certain organism, does not necessarily mean that

very serious effects can't arise from local activity of that infection. For instance, in subacute bacterial endocarditis, the immunity is high, the disease produces its effect in locally circumscribed areas, exudation is not characteristic, and skin tests usually show little effect. Why does the infection localize and produce such changes in the heart? Perhaps it is due to a massive clumping or agglutination of bacteria, which settle out in the end arteries of the heart valves. Once lodged there, in an area of relatively poor blood supply, the more central bacteria may be quite segrated from the immunizing forces in the blood stream, and able to gain a foothold. Rheumatic fever, on the other hand, shows marked sensitization — manifested by its wide-spread nature, exudative response and high reaction to skin tests in most cases.

We have now looked at a focus of infection and touched on three methods in which its disseminations may be given off and produce distant effects. These effects occur at certain times and only in certain people; one day the infection seems quiescent; the next, wide-spread effects are seen. One person is markedly affected by them; another reaches a healthy and ripe old age, despite frightful oral conditions. Obviously, many factors are at play and we can only mention a few which seem of especial import, once a focus has been established in tonsil, tooth, sinus, or middle ear. In thinking of these factors, we must consider them as casting their weight in favour of one of the two combatting forces, viz. the virulence of the infection and the resistance of the body.

Heredity is undoubtedly very important and is often neglected in reports on series of cases found in the literature, greatly detracting from their value. As we can have little influence on this factor, it shall not be elaborated upon.

The type of organism varies from case to case and must play a great part in the activity of any given focus. Here we are on dangerous ground and no figures can be quoted which would be of any practical value. Mention may be made however, that frequently (percentages differ in the literature) streptococci of the viridans type have been proven in tonsils and teeth, in cases of subacute bacterial endocarditis.

The factor of *age* must be stressed greatly in this connection, as in its relation to all diseases. Certain diseases have a predilection for definite age groupings and are not found in others. The reasons for such choices may be varied and complex. Changes in anatomical development and increased general resistance seem important. It is not necessary to mention many examples but two seem most striking. Recurrent osteomyelitis is a rare occurrence after maturity. I think that here the onus can be definitely related to morphological changes. The epiphyseal cartilaginous areas, the common sites for the original infection, have been removed in the older person. The latter may certainly develop osteomyelitis, of a most virulent type, but the tendency to form foci, from which future attacks may arise, has gone. Rheumatic fever rarely occurs, for the first time, after the age of puberty. Here, the explanation can't be given.

Factors have been mentioned which are certainly of interest in their relation to focal infections, but which have little importance as far as treatment, prophylaxis, and practical utilization are concerned. Let me now stress influences which are of equal import and where we, as physicians, may play a part. Control may prevent the formation of a focus or may remove tendencies towards activity. At the top of the list I place Fatigue.

Here, too, is a broad term which can be subdivided, rather inadequately perhaps, into voluntary and involuntary fatigue. As exemplary of the first grouping, let us consider the differences between the trained athlete with his daily workout and the sedentary student playing an unusual game of squash. Fatigue certainly results in both cases.

The first man, however, slowly trains for months, gradually warms up, has his rub-down and certainly avoids chills. He doesn't know that he is fighting off focal infections, but he is. Why is this suggestion made? Let's think of exercise physiologically in terms of the vascular system. Even moderate exertion produces the familiar results, the skin glows and flushes, perspiration follows, the mouth gets warm and waters, and so forth—all evidence of a migration to the surface by the blood stream, to the skin, the mouth, the tonsillar regions and so on, simply begging for a load of infected material or toxin. The muscular system can very well carry on with inadequate oxidation for the time being. Exercise over however, the shift is back towards restoration of the credit in the muscles and deeper structures—possibly to their detriment. Adding to this cycle the factor of extreme fatigue, with ensuing capillary damage by waste materials, exhaustion, or external cold, a plausible story is offered us. Fatigue may be apparent in other organs and systems as well—as an example, the gastro intestinal system. Various workers have shown that, with a few specific exceptions, bacteria cannot gain access to the body through the normal intestinal wall. The infectious diarrhoeas, or obstinate constipation may play a role in destroying this impregnability, by causing fatigue, congestion and capillary damage in those structures, providing ideal conditions for focal infections.

Of similar importance, and perhaps of even greater interest to the paediatrician is the question of diet. This is a field on which we can only touch. The practising physician well knows, and the student has heard repeatedly, of the effects nutritional upsets have on the susceptibility of the infant and young child to infections, and the converse is equally true. Clinical evidence is abundant in demonstrating the high incidence of rheumatic fever, nephritis, bacterial endocarditis, and many other sequelae to foci of infection, amongst the undernourished children. In experimental work carried out by the Staff of the Hospital for Sick Children, at Childrens' Homes, it has been found that the incidence of dental caries and subsequent infection was almost twice as great amongst those individuals showing a lack of Vitamin D in their diets. Many times, the occurrence of otitis media accompanying intestinal intoxication in infants has been noted. Although the Staff of the Hospital for Sick Children has, by careful work, ruled this out as arising from the intestinal lesion itself, no doubt the factors of nutritional disturbance and fatigue play a large role in this case. It is well recognized that various types of bacteria flourish well, badly, or not at all in accordance with the medium provided for them. Some grow extensively in an acid environment; others prefer alkaline surroundings; many flourish in the presence of much carbohydrate. Here is one aspect of bacteriological knowledge which has had little clinical application or trial. Many of us know only too well the crop of pimples which miraculously pop up, following excess of sweets. It seems to me that this observation, for instance, might certainly be applied to the clinical study of osteomyelitis in children. Has the amount of carbohydrate in the diet anything to do with the continuance of these foci in the bones? Can they be controlled by dietary changes? Can this lead be applied to infections arising from organisms other than the staphylococcus? Are we following incorrect principles in pumping 5 and 10% glucose into many patients suffering from any severe infective lesion, regardless of its etiology? These questions must be answered before the complete comprehension of this factor of diet and nutrition is attained.

Again and again, the relationship of trauma to the development of localized infections and to their dissemination to other parts has been mentioned. This may well be divided again into mechanical and environmental modes of traumatization. The first is obvious in

its results. The little boy bumps his shin, or twists his leg:—osteomyelitis appears for the first time. It is to be accounted for by increased vascularity, or capillary damage? I don't know but the fact remains that it *does occur*. The root of the tooth, exposed by chance to an infecting organism, provides exactly the sort of place suited to the latter. Heat, moisture and plently of good carbohydrate are there. Continual trauma with every movement of the jaw assists, not only in the continuance of the local infection, but in the dissemination to distant parts. In regard to this last statement concerning opportunities for dissemination, it might be interesting to note figures which were brought to my attention by one writer viz. (a). With every movement of the adult jaw, a biting force of 240 lbs. per square inch is applied to every tooth. (b) The great area exposed to absorption by the blood stream from a tooth root is 1.5—2 sq. cms. for each tooth.

To mention a secondary focus, where trauma seems to play a very important part. I would direct your attention to the heart valves. I am again unable to quote figures here, but it takes little imagination to formulate the importance of mechanical strain in the development of infections of these structures. The form of trauma resulting from environmental changes presents a less obvious picture and here conjecture must play a great part. We are dealing with the effects of heat and cold, dust, and lack of moisture, for example, on the normal resistance of the skin and mucosal surfaces of the body. The relationship of heat and cold to the shift of the bloodstream to and from the surface of the body has been mentioned before, definite capillary damage (temporary perhaps) in explanation of the favourable conditions for infection has been suggested. Probably just as important, in many cases, is the actual damage to the normally impregnable surface. The tonsillar mucosa, dried and cracked by heat and dust, forms an ideal entrance for infections. The various accessory nasal sinuses also are similarly affected.

We have now considered a few aspects of focal infection and must attempt to apply our theories to the clinical picture and to find support for them from evidence found in actual practice. Practically, this is extremely difficult to do, and the literature is full of contradictory reports on the value of removal of various foci. Of course, the answer lies in the neglect, by the contributors, of the various factors responsible, of the modes in which effects may be produced, and most important of all, of the fact that secondary foci are readily formed and may be the site of the actual trouble.

It is unnecessary to enumerate the varous accepted sites of foci of infection; they vary with different authorities; but most commonly the teeth, tonsils, middle ear and accessory nasal sinuses are incriminated as primary foci. The importance of the latter in children has been neglected greatly in many cases and it is only recently that several authorities have found them infected as frequently as in adults, and responsible for definite clinical symptoms and signs. The ready formation of secondary foci, of course, varies with many factors and conditions, but heart valves, joints, bone marrow, gall bladder, appendix and so on have all been mentioned and may be effective after removal of the primary focus.

Let us divide focal infection, as was suggested earlier in this paper, according to the route which may be followed in the production of the distant symptoms and signs, i.e.—(a) bacterial, (b) toxic, (c) allergic, and attempt to stress the importance of each route by a given clinical example. Though many others may be mentioned, subacute bacterial endocarditis comes to mind as the striking example of the first group. This disease, coming on often insidiously, seems to follow almost invariably a focus of infection somewhere in the upper respiratory tract, most commonly in the tonsils or adenoids. The other two methods of production of

symptoms and signs are readily ruled out; the immunity to the infecting organism is high, the effects tend to be localized rather than general, and the various organs and tissues don't show signs of toxicity. More important, all the necessary attributes of a focus and its effect are present. We have the primary lesion in the upper respiratory tract, from which organisms may be cultured. The same organisms may be found in the blood stream. Finally a definite secondary focus is found in the heart valves and again the same organism is isolated. The futility of attempting tonsillectomy in these cases is, of course, obvious.

The relationship of foci in the second group is not so clearly shown and into it we may cast many ill-defined conditions. General malnutrition and poor growth physically and mentally in children, as the result in many cases, of the toxicity dependent on infected tonsils, teeth, adenoids or sinuses may be suggested. No definite secondary lesion is found in many of these cases; blood cultures are, of course, negative; and sensitivity cannot be shown to be present. Yet, after removal of the infection, decided improvement occurs in the majority of cases. Even more striking, is the rarity of poor growth and malnutrition, all other factors being equal, if foci of infection are prevented, or early eradicated. Only one real bit of experimental work in this regard could be found but it is presented to you for what it is worth. Of 31 stock dogs, apparently healthy in every way, 7 were kept for controls. In 12 animals, the distal half of a tooth was removed, the core packed with cultures of streptococcus viridans, and the tooth sealed off. These inoculated animals, with 12 others, were studied under conditions of severe stress for a period of six months. The animals were all well fed and treated, but were forced to undergo severe exercise on a treadmill for 15 minutes daily. It was found that only 25% of the inoculated dogs were alive at the end of the course, and they in poor shape, while 83% of the controls survived, the others being killed by fighting. Throughout the experiment, it was noted that the inoculated animals were constantly more depressed and fatigued. Autopsy findings showed typical apical abscesses in the affected dogs and generalized signs of toxicity, cardiac hypertrophy, fatty degeneration in the liver, and cloudy swelling in the kidneys. No changes of note were observed in the controls. While it is unwise to argue from small numbers, and even more so to transpose animal results into human conditions, yet this experiment is highly suggestive.

Finally, though other examples may be used with a better basis e.g. asthmatic conditions) acute rheumatic fever, with a broad use of the term is cited as an example of the effect of focal infections acting allergically. Judging from the extensive clinical records, as found in the literature, it is difficult to prove this, but I am proffering it as the only theory which will satisfy many of the characteristics of that disease.

Many authorities, more particularly Swift and Coburn, state that rheumatic fever is a systemic disease manifested by reactions of different tissues, in susceptible individuals, to products of bacterial activity in the upper respiratory-tract. It is unnecessary to deal with the various forms that it may take, you know them well, but the fact should be stressed that, through them all, runs a common pathological and clinical picture. Clinically, exudation, widespread in character is commonly found. Histologically, this exudation is readily seen in sections made of the damaged tissues, coupled with the typical focal necrosis and endothelial proliferation commencing about the blood vessels. Swift goes so far as to suggest that these unfortunate individuals are perpetually in a state of sensitivity, initiated by the original infection and maintained by continual small emanations from an infected focus, which would produce no results in a normal person. The frequent exacerbations, which appear almost constantly follow-

ing mild upper respiratory infections, would tend to support this supposition. Many attempts at isolating the organism causing this disease have been made: many people have been convinced that they have found it: all show very convincing results, usually with different strains of bacteria. It seems probable that several cultural strains of the streptococcus play a part in initiating the conditions. This wide diversity in results and fairly constant negative blood cultures cause us to favour a more elastic allergic explanation. Finally, skin tests, which previously been mentioned (more especially those of Birkhaug(. show a high percentage of reactions to dead bacteria and filtrates; in rheumatic subjects, 75% positive, whereas normal controls give a positive result in about 30% of cases.

In attempting to find support for the present practice of eradication of all foci of infection in various diseases of childhood, and of maturity too, the results of Kaiser, made on long-continued follow-up of 5,000 tonsillectomized children and controls, are interesting. He found that, whereas tonsillectomy produced only a relatively small improvement amongst rheumatics, yet the primary attack of rheumatism occurs 33% less commonly in tonsillectomized children. In this series, nephritis is only one third as frequent in children following tonsillectomy. It is to be noted that his figures only apply to one possible focus—the tonsil. Other figures could be quoted in support of these, many could be mentioned presenting a different picture, but the essential point about most clinical results is that the great place for eradication of possible foci lies before the development of its secondary effects.

This is, more and more, the age of preventive medicine. Many of the infectious diseases are rendered impossible by early immunization. The much dreaded intestinal intoxication in infancy is decreasing by a proper understanding and application of sane feeding methods. The deficiency diseases are more and more rare. We appreciate or, at any rate, suspect the role of infected teeth, tonsils, adenoids, middle ears, and sinuses, in the production of more serious and killing diseases. Definite consideration of these danger zones in frequent and careful routine examinations, their eradication when suspected of infection, and more emphatic stress on the control of the various factors favouring focal infection should be the practice of every physician dealing with children.

In conclusion the writer desires to express his thanks to Dr. Alan Brown and to Dr. Holman for their help in preparing this paper.

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LUNG ABSCESS

By MAX O. KLOTZ, '35.

This condition may best be defined as a focus of suppuration occurring within pulmonary parenchyma and must be clearly differentiated from intrabronchial disease, such as purulent bronchiectasis. Thus the formation of an abscess requires necrosis of lung tissue accompanied by bacterial liquification thereof.

The problem of lung abscess is increasing as judged by the increasing frequency with which it is seen, particularly the post-operative forms.

Though the occasional abscess seems to develop without any antecedent factor, the majority follow (a) upper respiratory operation, (b) pneumonia and (c) Aspiration of a foreign body. Those who have investigated the subject are agreed that post-pneumonic abscesses account for 30% to 35% of all cases. They may be secondary to either broncho-, influenzal,, or lobar-pneumonia. In the case of the latter which is possibly the commonest, the abscess is the result of the secondary invaders. Reports as to the incidence of post-operative abscesses very greatly. Lord in an anlysis of 227 cases found 34% to follow tonsillectomy, while Moore estimates that abscess occurs only once in 2500 to 3000 tonsilectomies. Cutler found in his series of 1908 cases that 15% followed extra-respiratory tract operations. Abscess following the aspiration of a foreign body occurs most commonly in children, the peanut being the usual offender. Lung abscess is occasionally seen following the extraction of teeth, after chest injuries, as a secondary manifestation of a suppurating process elsewhere, and not infrequently as a complication of bronchiectasis. The relation of abscess development to sinus infection has not been satsisfactorily explained, but it would appear that the sinus involvement is as a rule secondary to the lung condition. There are but two theories as to the source of pulmonary abscess worthy of consideration, namely haematogenic or embolic and bronchogenic or aspiration theories. In a paper of this length, one can but briefly enumerate the evidence in support of each.

The following facts are used as an argument in favour of the bronchogenic origin of the lesion:—1. Abscesses follow, most frequently operations on the upper respiratory tract under general anaesthesia, less often after operations on other parts of the body and most infrequently when local anaesthetics are employed. 2. Experimental proof that aspiration does occur is common. 3. 60% of abscesses are found in the lower lobes, most commonly in the right lower, which is the site of election for the impaction of foreign bodies. 4. The organisms found in pulmonary abscess are by some, claimed to be identical with those found in normal oral flora.

In support of the embolic theory we have:—1. the occurrance of abscesses following local anaethesia, 2. the frequency with which they occur after operations in infected fields, including extra-respiratory operations, 3. the fact that pulmonary infarcts are commonest in the lower lobes, and 4. the fact that extra-respiratory operations which are followed by abscesses are usually on mobile parts which is in keeping with experimental findings.

The tendency here is in sympathy with the aspiration theory.

A study of the bacteriological findings are little help. Ermatinger in 1928 isolated a haemolytic staphylococcus aureus, a haemolytic streptococcus and the micrococcus catarrhalis most frequently and consistently, though other organisms were occasionally present.

Smith submits a very different group, including five strains of spirochetes, two strains of fusiform b a c i l l i, anaerobic streptococci and vibrios. Thus, from the above facts we see that no conclusions can be drawn as regards the etiology of this condition.

The morbid anatomy is fairly consistant in its essential details, but a division into acute and chronic types is necessary. Single abscesses are commoner though multiple lesions do occur. Like suppurating foci elsewhere, the abscess tends to be round and may vary from almost microscopic dimensions up to the size of an orange. On section the contents are of a thick yellowish or whitish colour, and may be of a blood strained nature with either a sweetish or foul odour. If acute, the walls will consist of soft necrotic ragged lung tissue, surrounded by intense hyperaemia and oedema. If the abscess should discharge at this point by one or another route, the necrotic material will slough out, the cavity walls will fall together and complete resolution may be the final outcome. The size of the cavity appears to have no relation to the resolving process. An abscess of longer standing will initiate a foreign body reaction in the surrounding tissue, with the result that thick fibrous walks are formed, encapsulating the purulent material. An abscess may terminate by 1. rupturing into a bronchus, and if drainage is efficient, healing. 2. Rupture into the pleural cavity with subsequent pyo-pneumo-thorax, may occur, or if adhesions have been previously formed an encysted empyema will result. 3. The abscess may become chronic if ineffectually drained or if a bronchial communication is not established, in which case very extensive carnification of the surrounding lung will occur because of the chronic pneumonia which invariably develops about the abscess and extends for a variable distance into pulmonary tissue. This pneumonia is further augmented by the foreign body reaction which occurs as mentioned above.

The development of symptoms associated with any of the known aetiological factors, particularly post-operative cases, should arouse ones suspicions. In a typical post-tonsillectomy case, symptoms usually make their appearance about the sixth day, being characterized by an intermittent type of fever, chills, sweating and a high leukocytosis. Frequently cough, expectoration, and, if the pleura is involved in the inflammatory process, chest pain are found. The sudden evacuation of a large quantity of foul or sweetish pus is extremely suggestive.

In post pneumonic cases the development of an abscess may be overshadowed by the symptoms already present. Thus if it occurs early in the disease, when cough fever and chest pain are probably present, the condition is likely to be found only at post-mortem. An abscess is seldom diagnosed early in pneumonia unless it bursts and a large amount of purulent material is coughed up. Later in the disease, if the patient's temperature should again rise after a decline, abscess should be suspected. Similarily if the patient's temperature remains elevated for an unwarranted length of time, and particularly if cough and sputum are present, ones suspicions should be aroused.

Following the evacuation of pus the constitutional symptoms usually diminish greatly in their severity. If this should fail to occur, it is as a rule an indication that drainage is inadequate.

The demonstration of elastic fibres in the expectorated material is indicative of destruction of lung tissue and points strongly towards the presence of an abscess. This test is usually positive about the thirteenth day after the onset of symptoms, which is also the time at which rupture of the abscess usually occurs.

Physical signs are seldom of much assistance in making a diagnosis. They may be entirely absent in a deep seated lesion or if present, may be masked by the primary pulmonary condition or an associated pleural effusion. The only

signs of any significance or aid, are those of cavity formation. In order to have these signs present, the cavity must lie close to the chest wall and be at least partially emptied of its contents. Under such conditions one might expect to find a localized area of tympany (with some dullness), whispered pectoriloquy and consonating rales, but any one or two of these signs may be absent. It is probable that somewhat less than 30% of cases reveal evidence of cavity formation on physical examination.

All cases in which the presence of an abscess is suspected should be given the benefit of an X-ray examination. The finding of a localized area of increased density, with a more or less centrally placed area of rarifaction, having a horizontal base is almost pathognomonic of cavity formation. Should the abscess be completely filled by the inflammatory products, it will not likely be visualized, hence it is wise under such conditions, to view the patient in various positions under the fluoroscope.

The most confusing cases in which to make a diagnosis are those postoperative patients in whom symptoms, for some reason or other, do not appear for weeks and even months after the instigating event has occurred. These cases may show relatively few constitutional symptoms in view of the gravity of their lesion. Tuberculosis and bronchiectasis are the two conditions most likely to be confused with this type of chronic abscess. A careful history to determine a primary factor, repeated sputum examinations for acid fast baccilli and X-ray examination should establish the diagnosis.

The prognosis of this condition depends somewhat on the antecedent condition. Thus an abscess developing in a pneumonic patient who is already debilitated and whose resistance has been sapped, is in a much more serious state of affairs than one developing in a healthy post-tonsillectomy case. Also the agents responsible for the lesion seem to vary considerably in virulence. These variations in virulence and resistance may explain the delayed appearance of symptoms in the occasional case. The prognosis also depends on the type of treatment, those cases treated entirely medically having a 50% mortality while surgical measures reduce this rate by half. How many cases are unrecognized and resolve spontaneously is not known.

Treatment is essentially that of any suppurating process anywhere in the body, namely to establish adequate drainage. During the acute stage no active surgical measures should be undertaken except when the constitutional symptoms fail to diminish and the patient shows signs of a rapidly increasing toxicity. The patient should be treated as a pneumonia with postural drainage added, the position being determined by the site of the cavity. Thus in a lower lobe abscess, the patient should lie on his good side for half an hour, in order that the contents may drain into the larger bonchi, then by

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depressing the upper half of the body they will be discharged into the trachea and expectorated with the aid of the cough reflex. Under such treatment a number of abscesses will become obliterated. How long this treatment should be carried on before surgery is introduced is difficult to say, and must naturally vary with the individual case. As a rule surgical drainage should be established when the state of the patient, as estimated by constitutional signs, makes him a good operative risk, or if the patient is unimproved or worse after medical treatment.

Drainage is usually obtained by thoracotomy and rib resection. The debris within the cavity is removed and large soft drainage tubes inserted. The operation is as a rule carried out in two stages, the pleural cavity being obliterated at the first to avoid the danger of an empyema developing.

Other surgical procedures may be dealt with briefly. In certain chronic abscesses, where the walls are fibrosed to such an extent that they are not likely to become opposed, which is essential for healing, lobectomy is indicated. These cases often have little disability but because of their copious foul sputum are decidedly unpleasant to themselves and everyone else. Similar treatment is indicated where the abscess is too extensive to be drained or where there are multiple cavities confined to one lobe.

Pneumothorax has often been used in an attempt to evacuate the cavity, but it is not without danger as rupture into the pleural cavity is a not uncommon sequel. Furthermore it is impossible by this means to collapse a deep seated cavity and the difficulty is usually added to by the presence of adhesions.

Phrenicotomy is not advisable because the collapse is insufficient to obliterate the cavity. Also it is often followed by varying degrees of upper intestinal obstructions, according to some workers.

Thoracoplasty is only applicable in multiple abscesses involving more than one lobe but confined to one side of the chest, and occasionally where healing is prevented by the fibrosed condition of the cavity wall.

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RHEUMATOID AND OSTEOARTHRITIS

By B. CAMERON BLACKHALL, '35.

Introduction:

This paper was undertaken with the ultimate object of presenting to students a fundamental and useful conception of these two great divisions of arthritis. The author makes no apologies for grouping the aetiology and treatment of these conditions under general headings, since our present knowledge of the subject matter does not warrant a different method of approach.

Rheumatoid arthritis is called proliferative arthritis in American nomeuclature, chronic poly-arthritis on the Continent, and Atrophic Arthitis by Goldthwait, while Osteo-Arthritis is considered as a Degenerative Arthritis in American literature and Hypertrophic by Goldthwait. The author does not believe that there is anything to be gained by sub-dividing the main divisions into sub-groups since it adds needless confusion to a somewhat chaotic subject.

Aetiology:

Women are more frequent sufferers from rheumatoid arthritis, but the incidence of osteo-arthritis is approximately equal in both sexes. The rheumatoid syndrome is common in women of the reproductive period. Osteo-arhtritis occurs most frequently between forty and seventy years of age. Wide variations in temperature, especially if combined with considerable dampness, is undoubtedly a factor, but osteo-arthritis is more prevalent in a hot dry country. Occupation appears to play no definite part in the aetiology of these conditions. An imbalance between hormonal secretions is thought to be a causative factor. Hyperthyroidism is frequently present in rheumatoid arthritis, and hypo-thryroidism is observed in osteo-arthritis. Allergic sensitivity undoubtedly is a factor in some cases but its relation is as yet unknown. Considerable work has been done by Fletcher and others, which indicates that a condition of avitaminosis frequently exists in arthritis, a lack of vitamin B being especially common.

Extensive research has been done by American investigators, notably Cecil, on the focal infection theory. The evidence available, though by no means conclusive and entirely substantiated, points to the streptococcus viridans type of organism as an aetiologic factor, but staphylocci, or the colon group are occasionally concerned. The following areas are the sites of election for infective foci: Apical infection of the teeth is very important and capped teeth should be regarded with suspicion; radiological examination is often necessary in these cases. Tonsilitis is common and arthritis due to tonsillar infection is prevalent in young people. It is not relieved by salicylates, and no evident carditis is present. Of the nasal sinuses the maxillary antrum is the chief offender, and in doubtful cases antral puncture, and examination of washings in indicated. There may be a chronic rhinitis and Pharyngitis apart from antral or tonsillar infection. Chronic infection such as cholecystitis, appendicitis and diverticulitis may be present. In the male, the urethra, prostrate and seminal vesicles should be investigated. In females gonorrhoea is frequently a factor, and cervical erosions not necessarily Neisserian in origin should be treated.

From the above it will be gathered that there are few areas of the body which are exempt from focal infection, and hence its role as a basic aetiological factor is as yet problematical. It is becoming more self-evident that there is no single causative factor producing arthritis. Rather there exists a

widely disturbed physiology, which can not be corrected by any single measure.

Clinical Features.

Rheumatoid Arthritis. Prodromal symptoms such as muscle weakness, cramps, paraesthesiae, or vasomotor instability may be present in a female of child-bearing age. The onset may be acute or sub-acute with febrile or subfebrile temperature in association with enlargement of one or more small joints of the hand, wrist, elbow, toes, ankles and knee. The joints are fusiformely swollen and usually very tender in the early stages. Muscular wasting may be pronounced especially in the small muscles of the hand. As the disease progresses, stiffness, contractures, and even ankylosis may be present. Typical ulnar deviation is observed in the hands. The progress is centripetal in nature, and the disease bi-laterally symmetrical. The general health of the patient is usually poor, pronounced anemia is often observed, as is tachycardia, sweating or coldness of the extremities. On X-ray examination, osteoporosis is often noted and may not be confined to the ends of the long bones. Improvement may or may not be noted after the removal of septic foci.

Osteo-Arthritis. The disease begins in an elderly individual of either sex, and has a predilection for the larger joints. When a single joint is affected, it is rare to find any signs of preceding inflammation, but if several joints are involved, such a history may be obtained. The essential changes are degenerative, followed by bony hyperplasia, which may or may not cause symptoms. As previously stated, the disease occurs in elderly individuals who may be otherwise healthy, but in whom arteriosclerotic and degenerative changes may be noted. The earliest symptom is stiffness experienced after rest, and disappearing on movement. Pain may be quite absent, but if the weight-bearing joints are affected, it is common, particularly after prolonged activity. The joint is puffy and tender. In the initial stages on active or passive movement, a soft creaking, later giving place to a coarse grating can be elicited. Muscular spasm restricts movement, and the muscles about the joint waste to some extent. Marked bony proliferation giving a totally altered and grotesque appearance to the affected joint is frequently observed. There is usually no improvement noted after removal of foci of infection.

Pathology

Rheumatoid Arthritis. This disease starts with a lymphocytic infiltration into the synovial membrane, which is most marked at the margins. The synovia proliferates and fresh granulation tissue is formed, which extends as a thin pannus over the joint surface of the cartilage. Coincidentally there is a proliferation of the endosteum of the epiphyseal sub-chondral area, with the formation of an advancing line of granulation tissue and bony trabeculae. Hence the cartilage is attacked from two sides, and is gradually replaced by a granultomatous mass. Depending on whether the synovial pannus, or the endosteal or perichondral proliferation predominates, a fibrous or bony ankylosis is produced. In the initial stages the synovial fluid is increased, there is leucocytosis, and usually hyperpyrexia; in later stages with a disappearance or diminution of joint cavity the joint fluid is lessened in amount or absent. The capsule is infiltrated by lymphoid cells, new vessels are formed, and fibrous tissue is laid down with the resultant peri-articular thickening. The lime salts of the bone are absorbed leading to a rarefaction and a decrease in density.

Osteo-Arthritis is characterized by a degeneration of hyaline cartilage with a resulting hypertrophy of cartilage and bone of the joint as a unit. The initial lesion is a fibrillation of the cartilaginious matrix at right angles to the surface. The cartilage becomes softened and eroded, and the bone is exposed.

Associated with the degeneration of cartilage and bone in one area, there is a corresponding proliferation of opposite bone, and an attempt is made to preserve a joint surface, even though it is extremely irregular. The cartillaginous degeneration is a slow process, usually unaccompanied by any fever, leucocytoss or joint effusion, and as a result of the chronicity of the lesion, and the nature of the joint surface, motion is usually well preserved in some directions, and distinctly limited in others. In long standing cases the endosteal trabeculae become thickened, the narrow spaces are nearly obliterated, and this leads to an increased density of articular surface, and as a result of pressure eburnation is produced. In these degenerative cases proliferation of bone is common, and at the periphery of the joint, where the cartilage and capsule meet, there is usually a marked perichondral proliferation, and obvious bony lipping is produced.

Dynamic Pathology:

In conjunction with the typical pathology just outlined, considerable effort has been expended on the dynamic or living pathology of these diseases; a brief review of which may not be out of order. No deviation from normal can be demonstrated in fat metabolism, non-protein nitrogen, uric acid, or creatinine content of blood. Due to the nature of bony changes, one would suspect an altered calcium, phosphorus, or phosphatase content n blood but none is observed. The CO_2 combining power in rheumatoid arthritis tends to be five to seven per cent. below normal. Some workers believed that arthritic manifestations were caused by an accumulation of lactic acid in the body. Recent work shows that blood, urine, and sweat are normal for lactic acid content. Pemberton reports a slight delay in salt and water excretion, but other workers do not substantiate this view.

Many workers have observed achlorhydria in seventy per cent. of arthritics. This high incidence is not generally accepted; however, at least twenty to thirty per cent. of these patients show hypochlorhydria, which is five to six times higher than is observed in normal people. The lessened hydrochloric acid is duplicated by other diseases, and the difference is too small to warrant definite conclusions. Fletcher has observed that many arthritics show a definite type of colon on radiological examination. The colon is longer, wider, more convoluted, and reduplications are present. This picture is common in the tall, thin, visceroptotic type of arthritic. Seventy per cent. of these people are chronically constipated, and complain of aching pain in the left lower hypochondrium.

The rheumatoid group have the highest sedimentation rate, falling below fifty in one half hour or less, and in those cases which show improvement clinically and symptomatically, the sedimentation rate changes only slightly, indicating that the subjective improvement is only local and that the basic condition is unchanged.

Pemberton, in a series of four hundred cases of rheumatoid and osteo-arthritis, reported that sixty per cent. showed a delayed sugar removal from the blood on the administration of glucose. The blood sugar curve increased normally for thirty to forty-five minutes, and then decreased at a slow rate, producing a characteristic lag. Glycosuria is rarely observed. Pemberton showed that if infective foci were removed, and the patient recovered from his arthritis the blood sugar curve returned to normal. It has been observed in arthritis that in performing the sugar tests, there is a rise in percentage saturation of blood with oxygen, and this means that either blood fails to reach the tissues, or the blood flow is accelerated. To test the increased rate theory in arthritics, it was supposed that absorption from the gastro-intestinal tract might be unduly rapid; this might account for the delayed sugar removal and the benefit of the caloric diet. Urea and potassium iodine were

fed with glucose. The blood and urine were analysed at thirty-minutes periods for N.P.N., urea, iodides and total nitrogen. No change was observed in these values in cases of arthritis with delayed sugar removal, as opposed to normal persons. Hence one is forced to the conclusion that the blood inadequately reaches the tissues.

To test the assumption that the blood inadequately reaches the tissues, the limbs were elevated in a group of four hundred arthritics, and in a normal series. Of the forty per cent. of arthritics, who normally do not show a delayed sugar removal, some sixteen per cent. of these show this phenomenon if the blood supply to the limb is interfered with. This is not observed in normal individuals. Hence seventy-six per cent. of arthritcs have a potential delayed sugar removal from the blood, and of the sixty per cent. who showed the lag in Pemberton's series, all were temporarily restored to normal by the use of vasodilators.

In view of evidence in favour of a relation between focal infection, arthritis, and delayed sugar removal, there is reason to believe that certain capillary areas are closed in arthritis. If this evidence is coupled with the relief obtained by measures increasing circulation, such as massage, the evidence is even stronger. By the use of the capillary microscopic method, it has been shown that many capillary areas are collapsed, and the flow is sluggish or intermittent in these diseases. Low red cell counts were observed on making stab wounds about arthritic joints. Normally the first drop of blood has a higher count than succeeding drops. In arthritis the first drop gives a considerably lower count than is normally observed. It has been shown that exercise produces acidosis, heat alkalosis, and massage does neither; hence the benefits accruing from these methods of treatment have not a chemical basis, but their efficacy is due to the fact that they all produce an increased circulation. As a very pertinent corollory to this it might be said that a disturbed circulation plays a predominant part in the pathology of these diseases.

Treatment:

Introduction. It is this phase of the disease that the medical profession have sadly neglected. This is due in no small measure to the intricacies and ramifications of the problem of the arthritides. Successful treatment can only be gained by a broad knowledge of the subject of helpful therapeutics, combined with the fundamental knowledge of the individual case. Due to the fact that there appears to be no single panacea for these conditions, the profession have relegated them to the limbo of the unprofitable, and the public have looked elsewhere for help. If any of my readers will not deign to use or prescribe massage and other physiotherapeutic measures for their patients, then they will lose innumerable cases and the progress for control of these formidable diseases will be further retarded by their diffidence. Attention must be paid to the inciting factor such as bacteria, their toxic products, or the presence of allergic reactions. However, the general condition of the patient must not be lost sight of, and conditions producing malnutrition, over fatigue, or an unsuitable environment must be corrected. While chronic sepsis is not invariably followed by arthritis, it is not unreasonable to suppose that it may have deleterious effects on metabolism and endocrine function. On the other hand no focus may be demonstrated, and the trouble may be due to viamin deficiency, altered metabolism or endocrine dysfunction.

Vaccines. Autogenous vaccines are preferable if properly made, and are derived from the causative focus. Stock streptococcal vaccines have produced excellent results in the hands of Cecil and his co-workers. If an infected focus is suspected, and one is using a stock streptococcal vaccine, the initial dose should be between twenty and fifty thousand, and five hundred thous-

and if no focus is evident. Injections should be given in increasing strength every five or six days until signs and symptoms have disappeared or abated. Shock therapy using typhoid vaccines has been tried on the continent with indifferent success. Intramuscular injections of milk in 5 c.c. amounts have been used successfully in Germany.

Drugs. For analgesia sodium salicylate, and aceto-salicylic acid in ten grain does P.R.N. are useful. Phenacetin, five to ten grains, with caffeine citrate one to two grains, and amidopyrine five to ten grains are beneficial. Codeine one sixth to one-third grains combined with five to ten grains of phenacetin, or ten grains of aspirin is also helpful. Sodium and potassium iodide from five to ten grain doses, or mild tincture of iodine in five to ten minim doses taken in milk is good. Tonics such as cod liver oil and vitamin preparations are also indicated. Since anaemia is invariable in chronic cases, syrup of ferrous chloride in two drachm doses t.i.d., or reduced iron grains ten t.i.d. is efficacious in combatting the anaemia.

Endocrine Dysfunction. Evidence of hypo-thyroid stigmata should be looked for, and thyroid extract in one-half to one grain doses is administered daily till improvement is noted. In young women there is often a suppression of the menses with the onset of arthritis. In older women there is a premature climacteric when arthritis appears. Both these conditions for reasons not wholly understood respond to the use of the diathermy and the intra-pelvic electrode.

Diet. Much has been written about the diet in arthritis. The concensus of opinion appears to indicate that a well-balanced diet is essential. Obviously if a person is sensitive to certain foods, they must be eliminated. If they are over-weight and near the climacteric, the caloric intake, notably the carbo-hydrates should be restricted. A diet with slightly reduced carbohydrate, high in vitamins and minerals, and not constipating is essential. Fletcher reported an interesting series of cases, which showed the arthritic type of colon, and this was restored to normal by a reduced carbo-hydrate intake, high Vitamin B content, with the removal of focal infection.

Physiotherapeutic Treatment. The objects of this type of therapeutics are (1) to act as an anodyne, (2) to promote sweating and regulate capillary circulation, (3) to promote absorption of old inflammatory exudates, reduce periarticular thickening, and restore mobility to joints and muscles, (4) to regulate body metabolism, and elevate a lowered temperature if noted, and stimulate the defence mechanism of the body. This can be achieved by (1) heat or cold (2) massage, (3) active and passive movements and exercise.

Heat over 110° F. applied either locally or generally by means of hot pack, hot air, hot vapour, or diathermy has a local and a general effect on metabolism. It increases peripheral capillary circulation, promotes sweating, and resolves inflammatory thickenings. Massage is excellent for the elimination of adhesions, removal of fibrous nodules, restoration of muscle tone, and increasing circulation. If used indiscriminately it is harmful. If a joint is acutely inflamed, massage and movement are contra-indicated. The initial movement should be active to lessen the chance of joint injury, and any sign of returning inflammation is a signal for subsequent rest. In osteo-arthritis, movements should be carried out without weight bearing, and a hot bath is excellent for this procedure.

Electricity and Radiation. Diathermy is helpful in osteo-arthritis of large joints, especially the hip and knee. The relief from pain is often striking. In women, if there is any suspicion of pelvic infection, intra-pelvic electrodes are indicated. Ultra-Violet Rays have a general effect in that they increase resistance to infection, and have a definite tonic value. One to two minutes over a local area is sufficient for an initial exposure. Ionization is helpful in certain allied arthritic con-

ditions such as bursitis and fibrositis. Faradism is helpful in the treatment in muscle weakness and wasting.

Mineral waters and baths are extensively used in England and on the continent in the form of spa treatment, and are of undoubted value. Advanced renal, cardiovascular, tuberculosis, or malignancy, are contra indications to spa treatment.

Orthopaedic and Surgical Treatment: *Hip Joint.* The joint should be put at rest in acute stages. If the patient uses the joint for weight bearing, then progressive flexion and adduction deformities are invariable. In the active stage of the disease, where pain and muscle spasm are pronounced, rest and traction are essential until the active process subsides. Later the patient may be allowed up with crutches, but on no account must weight-bearing be attempted. At this stage gentle massage combined with abduction and extension is indicated, always keeping the movements well within the causation of muscular spasm or pain. Faradic stimulation of the muscles is beneficial. A walking caliper is useful, allowing the patient to get about, but restricting movement. If the process is quiescent, and the head of femur and acetabulam have not been extensively damaged, gentle manipulation under anaethesia will indicate whether the restricted movement is due to adhesions or muscle shortening. This treatment followed by heat, massage, and active weight-bearing do much for the patient. If muscle shortening is present tenotomy and splinting is undertaken. Should the disease be progressing, and there is considerable pain, then one must consider a fixation of the joint, or some type of Whitman's reconstruction, always tempering your decision by the patient's age and general condition.

Knee Joint. The deformities observed are external rotation from biceps contraction, flexion, and posterior luxation of the head of the tibia. In early cases rest and traction are indicated, always pulling in the line of deformity, and changing the angle slightly when the range of movement permits. If there is marked flexion, then Jone's method of lengthening the hamstrings is undertaken, or a transverse osteotomy and splinting may have to be resorted to. If considerable deformity is present, a Gritti-Stokes amputation is desirable.

Ankle and Foot. In these joints optimum movement and position are essential to preserve the proper function of the lower extremities. If the chance of ankylosis is imminent in the early stages, the foot must be immobolized in dorsi-flexion and slight varus. Positions of equinus, valgus, calcaneus are not to be tolerated if they possibly can be corrected. In all manipulations one should bear in mind the risk of lighting up the infection, and one should wait from six months to one year before manipulation is attempted. A preliminary course of massage will help you to gauge the quiescence of the nifection. Hallux Valgus is frequently

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observed and may be corrected by a Mayo type of operation. Metatarsalgia is not infrequently a complaint, and a careful examination may reveal, hyper-extension of the toes, a flattened transverse arch, and a swelling of the metatarsal joints. These cases may be very intractible, or amenable to the correction of faulty function by the use of a metatarsal bar across the sole behind the heads of the metatarsal bones, or a bevelled leather elevator covered with felt may be placed in the shoe, and fixed with adhesive. If flat foot is present then a proper plaster mould of the foot must be made, and a Whitman's arch support prepared.

Shoulder and Elbow. In these joints, if ankylosis is inevitable, the optimum position for the former joint is sixty degrees abduction, the arm being parallel to the body, and the forearm externally rotated twenty degrees from the horizontal; hence the patient is able to feed himself by scapular movement. The elbow should be kept active as long as possible, but if ankylosis is probable, 100 degrees extension, and fifteen degrees short of full pronation is the best position; if both the joints are affected, then one should be less than ninety degrees in extension, and the other greater than one hundred degrees.

Hand, Wrist and Fingers. Much can be done to these joints by splinting and physical treatment. To prevent spreading of carpal bones in elderly people, a leather wristlet is useful. If flexion and ulnar deviation are present, gentle manipulation under anaesthesia, and a cock-up splint gives good results. If stiffness and limitation of movement of the fingers has occurred, on no account must these joints be forcibly manipulated, as disaster usually follows in the shape of a more severe deformity and contracture. Deformed fingers should be treated by intermittent traction in the line of the finger, a five-ounce weight being sufficient. The patient is instructed to move his hands, and as the range of movement is increased, the line of traction is changed in the direction of flexion until a full range of movement is produced.

Summary.

A brief review of the salient features of the aetiology, diagnosis, pathology, and treatment of rheumatoid and osteo-arthritis has been presented. The author has written in general terms, since the knowledge of these conditions at the present time justifies no other presentation. Specificity has studiously been avoided, since the very nature of these diseases makes such treatment not only unwarranted but dangerous.

The writer will feel amply rewarded if this article tends to clarify in any respect the view-point of his fellow-students, on the much neglected and vexed question of rheumatoid and osteo-arthritis.

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SOME CLINICAL ASPECTS OF AMYLOID DISEASE

By R. P. DOUGLAS, '35.

Amyloid as a clinical entity in nearly every case is secondary to a chronic suppurating process of long standing, or it may be found to a lesser extent following such chronic cachechtic conditions as chronic nephritis, tumours, syphilis and various other similar diseases. In recent years it has been possible, if not to completely cure such afflictions, to at least alleviate them, and by this means the incidence of amyloidosis has been considerably reduced, so that now the only places where it is consistently found is in tuberculous sanitaria and homes for the incurables. Since the disease is so essentially a secondary condition, it is only natural that the age and sex incidence will follow closely that of the causative agent, while the distribution will be related to the same factor.

The liver, spleen and kidney are the three organs most commonly affected but the deposits may be found in any tissue, not excepting the brain, and there may be any combination of the locations. The process is generally considered to be a dysfunction of the fibroblastic elements wherein they are caused to produce the so-called amyloid material, which is slowly deposited in the neighboring tissues, and acts on the other cells by producing a pressure atrophy with their consequent death. Paradoxically, the organs affected, despite the tissue destruction, gradually enlarge. Thus one finds the liver slowly increasing in size and showing smooth, rounded edges, while the same holds true for the spleen, which may become definitely palpable.

The clinical findings are related chiefly to the lesions in liver and spleen, which, due to their great increase in size, produce a protuberance of the abdomen, and if the liver has been sufficiently embarrased there may be a prominence of the superficial veins, or even a certain amount of ascites. As well as this, one finds emaciation and a secondary anemia, but these are not so much due to the amyloidosis as to the etiological disease itself. If the kidney has been affected, as very frequently is the case, the urine will be found to consistently contain a considerable quantity of albumin. This escapes from the blood because of the glomerular damage and is often excreted in sufficient quantities to produce a slight lowering of the serum proteins. Unfortunately this picture, particularly if accompanied by a chronic pus producing process, which is so very diagnostic, is the exception rather than the rule. These findings, but to a lesser degree, are very apt to be discovered, but the absence of any one, or even two, of them cannot exclude the possibility of amyloid. Thus it is easily seen that if one is dependant on a physical examination alone there is a very good possibility of entirely missing the diagnosis.

This difficulty has been overcome during the last few years by applying the long known fact that amyloid picks up, and is stained by congo-red. Various investigators applied this information by injecting the substance into the circulation and estimated the percentage of the dye remaining in the sera after a given period of time. To do this they injected ten to fifteen cubic centimetres of a one per cent aqueous solution of the dye, the amount depending on the weight of the individual, and after allowing four minutes, which is the time it takes the congo-red to disseminate evenly throughout the plasma, they withdrew five cubic centimetres of blood. At the

end of another five minutes a further sample of five cubic centimetres of blood is taken. The sera of these two specimens are compared colourimetrically and the percentage of the dye lost is thereby determined. The normal rate of disappearance is twenty to thirty per cent in one hour, and therefore anything above that may be considered due to amyloid deposits. Nephrosis, by excretion of the dye also gives increased figures but these never go higher than sixty per cent. Therefore if in one hour one hundred to sixty per cent of the congo-red disappears, one may conclude that amyloid disease is present, while if the figures are from sixty to forty, nephrosis must be excluded. It is unfortunate that a negative result is far from being complete evidence that there are no amyloid deposits, but as it requires a certain amount of the material to absorb sufficient dye to show a result, it is obvious that with only a little amyloid you will get but a small loss of congo-red.

The possibility of reabsorption of amyloid material after having been layed down is a rather interesting one. Experimentally it has been shown with mice, that if the process is not allowed to go far, and all injections of sodium casienate, (the medium used to produce the deposit) are stopped, and the animals are fed on powdered whole liver, the substance will regress and disappear. This has been borne out clinically by Whitbeck who had a series of six cases of surgical tuberculosis, who, under the very best of modern tuberculous treatment plus powdered whole liver, succeeded in ridding themselves of the most marked signs of amyloid disease, including extremely enlarged liver and spleen as well as clearing their urine of albumin. The only fact that makes the picture incomplete, is that they were all positive with congo-red not only before, but after the disappearance of the clinically diagnostic features. No one has attempted to explain this fact. Walker, another observer, presents a case of a boy with empyema on whom a very radical and extremely successful thoracoplasty was carried out, and who having shown the classical evidence of amyloidosis before the procedure,, was absolutely rid of all diagnostic signs in four years. What one can conclude from these findings is very difficult to say, but it is the opinion of the writer that for the present at least, one should not promise patients anything definite as far as the alleviation of the amyloid is concerned.

Summary:

1. The relation of the incidence to the etiological factor is indicated.

2. The chief sites of amyloid deposit and its action on the tissue is discussed.

3. The important clinical findings are shown to be enlarged liver and spleen with albuminuria, and the difficulties of diagnosis, due to the inconsistency of the signs, is pointed out.

4. The method of using congo-red as an aid to diagnosis is discussed.

5. The possibility of a treatment to cause reabsorption, by radical removal of the foci and by giving powdered whole liver, is suggested.

THE ETIOLOGY OF GALL-STONES

By PAUL HAMILTON, B.A., '35.

The usual explanation offered in the texts for the presence of gall-stones, on a final analysis turns out to be rather indefinite. In fact the impression is gained that they "just growed up like Topsy." The explanation offered below will be seen to have a fairly sound biochemical basis and though all the factors may not be taken into consideration, yet a working hypothesis is submitted which gives every indication of being the key to this medical and surgical problem.

The foremost worker in this field has been E. Andrews in the United States. He investigated the bile salt-cholesterol ratio in both human beings and animals and found that in the dog this ratio was about 100, while in the human it was about 30-40. This ratio could be varied by the liver secreting less bile salts or by the gall-bladder absorbing bile salts faster than normal, and it was found that when the ratio approached 13 cholesterol precipitated out. This confirmed the statement that the bile cholesterol is held in solution by these salts, but Andrews went further and demonstrated the bile salts formed complex addition compounds with cholesterol. This he did by re-synthesis of these complexes. And it was also found that the complexes with taurocholic and desoxycholic acids were stable and resisted destruction by dialysis, whilst the other bile salt complexes, of which glycocholic acid is the chief, were easily broken down by this method, the salts being removed and the cholesterol being precipitated out.

The next step in the argument was to determine whether the bile in the gall-bladder had cholesterol added to it, or bile salts taken away. By tying off the cystic duct in a dog and leaving it for a period of days, it was found that the amount of cholesterol present was the same as the day that the duct was tied off. That is, no cholesterol was secreted by the gall-bladder mucosa. But the bile salt concentration was greatly reduced and the cholesterol was found in a finely divided state throughout the bile. From this work it was concluded that absorption of the bile salts by the gall-bladder mucosa was the chief factor in disturbing the bile salt-cholesterol ratio. And it was further found that anything which damaged the mucosa of this viscus caused a more rapid absorption of the bile salts, e.g., stasis or infection.

It must be admitted that other workers don't agree with Andrews in the non-absorption or non-secretion of cholesterol as indicated by him; namely Wilkie and Doubilet of Montreal. But in a review of the literature on the physiology of the gall-bladder, Ivy (Physiological Reviews 1934) leaves the impression that if the exchange between blood and bile via the gall-bladder wall does take place, it is almost negligible.

Here then is a method by which cholesterol may be precipitated from the bile. Stone formation is the next step and this according to Weiser and Gray is due to the solution of the cholesterol in the fat droplets which exist as an emulsion in the bile, to form a super-saturated solution, from which interlacing needle-like crystals of cholesteral are precipitated out. In support of this they claim that they were able to make synthetic stones almost identical with the human metabolic type of stones. It has been found too, by many workers that a badly damaged gall-bladder will secrete large quantities of calcium, and if cholesterol stones be present calcium will be deposited on the periphery. This then is a ready explanation for the formation

of the calcium-cholesterol type of stone. That cholesterol is the chief component was shown by Peel years ago, that all human stones have at least 80% cholesterol content. Since the bile pigments are also held in solution in part by the bile salts, it is not surprising that some pigment is incorporated into the stones.

Clinically Andrews backed his theory by showing that autopsy and surgical material from gall-bladders which contained stones, had a bile salt cholesterol ratio well below 13. And he also accounted for the fact that stones are very rarely found in the dog, because as stated before the ratio is about 100, a long way from the critical point.

The above explanation accounts for the fact that bacteria, tissue debris, etc., are found incorporated sometimes in the stones. They have been present at the time the cholesterol precipitated and have become associated with this small nucleus and thus are made a part of the stone. That is, these so-called nuclei of bacteria, etc., cannot, and do not form stones unless the correct biochemical setting is present. But if the appropriate chemical setting is present they may be incorporated in the precipitated materials. This agrees with the contention of Aschoff and Bacmeister who claimed that such particles were not in the centre of the stones and hence could not have been the cause of stone formation. The theory offered by Boyd seems untenable in the light of this work. He claims that cholesterolosis occurs and a cholesterol laden bit of mucosa is pinched off to form a nucleus for stone formation. But if according to Andrews the bile salt-cholesterol ratio were above 13, this should not cause stone formation but the reverse should take place. This contention is substantiated by the finding of Ivy and Walsh that human stones, if placed in a dog's gall-bladder disappear providing the gall-bladder drained normally. If the viscus became infected no reduction in size of the stone was noted.

Having investigated the mechanism by which stones were formed, the next step was to determine what factors were responsible for the damage necessary to cause an upset in the bile salt-cholesterol ratio. Since adequate drainage of a viscus is essential to the proper functioning of that organ it was reasonable to suspect stasis as a cause for damage to the gall-bladder. And it is obvious that infection would be a factor. And such proved to be the case. Many workers have found that when the cystic duct is ligated in the dog, it is very difficult to keep the gall-bladder from becoming infected. The argument has not been that infection took place, but the route by which the bacteria gained entrance to the viscus. There are four such possible routes, (1) by the blood stream, (2) by direct extension by way of the lymphatics from neighbouring organs, (3) by retrodrage invasion up the common duct, and (4) by bacteria excreted in the bile by the liver. These last two routes are not considered by most authorities because of much evidence to the contrary, but greatly divergent opinion exists concerning the haematogenous and direct extension routes.

The selective action of bacteria, carried in the blood stream, was first enunciated by Rosenow. His work has since been strengthened by Wilkie. This latter worker, by culturing the cystic duct gland, which he assumed to receive the total lymph drainage from the gall-bladder, obtained a strain of streptococci which on being subcultured, was capable of producing a cholecystitis in rabbits, when the living organism was repeatedly injected into the ear vein of that animal. And further, to an objection raised by Evarts Graham, the gall-bladder was isolated from the liver in some cases, by interposing a piece of omentum between it and the liver bed. The results were the same; a cholecystitis assumed to be of hepatogenous origin developed.

This work is not very conclusive however. The anaerobic type of or-

ganisms were not cultured, the state of the liver was not investigated and the assumption that the lymph drainage of the gall-bladder is entirely into the cystic duct, is entirely wrong. Several workers have found that B. welchii can often cause cholecystitis, especially the acute variety. And many authorities claim there is an intimate lymphatic and venous connection between those of the gall-bladder and those found between the liver lobules. Graham has even demonstrated the close lymphatic connection by injection methods. That an important error arises from not examining the liver tissue will be seen from some of the work cited below.

Graham, Judd, and Flint have found that if sections of liver are removed at operation when cholecystectomy is done, and examined microscopically, evidence of a hepatitis can be found in every case. This consists of some fibrosis, round cell infiltration and some oedema in the portal areas and along the intrahepatic bile ducts. There are serious objections to these statements for the following reasons. Since the liver is the chief organ in removing bacteria from the blood stream (because if extirpated bacteria are only very slowly removed from the blood stream), and since, as Arnold has shown, there is a continual infecting of the thoracic duct via the lymphatics from the intestine, it follows that in order to handle this varying bacterial seeding, the cell picture in the liver must needs change from time to time. Hence it is very difficult to establish the normal picture of liver. And secondly, since a patient may have other conditions as well as the cholecystitis, which may have an effect upon the liver, the relation between gall-bladder disease and the condition of the liver cannot be correlated accurately till it is known what other conditions effect the liver, so they may be taken into consideration.

Andrews however, by ligation of the cystic, common duct or both, in dogs, found that a cholecystitis developed which began on the hepatic side of the viscus, the peritoneal or free side remaining clear. The inflammatory process gradually extended around the whole viscus, and was seen to attack the outer layers of the gall-bladder first, the mucosa being the last structure to be damaged. He further found an associated hepatitis which was at first noticed in the region of the gall-bladder. From these results Andrews argues that the infection was of hepatic origin especially since many of his dogs had a cholecystitis caused by the anaerobic flora of the liver. His work has also definitely shown that mere stasis will cause the gall-bladder to become infected.

Some attempt may now be made to link up the above facts to explain the process by which gall-stones are formed. Due to a disturbance of the bile salt-cholesterol ratio, cholesterol may be precipitated out, and in the presence of emulsified fat particles, is formed into stones. The bile salt-cholesterol ratio may be disturbed by the excretion of a bile at or near the critical point for this ratio. More frequently however it is due to the rapid absorption of bile salts from the gall-bladder because of damage to its mucosa. This damage may be caused by mild infection or chronic stasis of a mild type. As a result, stones are formed and infection, if it has not already taken place, will occur if the stone blocks the cystic duct. With the infection of the gall-bladder there arises an associated hepatitis. The badly damaged (functionally) mucosa secretes calcium carbonate and so a mixed stone is formed.

The question of the chronic stasis of the biliary system mentioned above is an interesting one, and might be discussed still further. Since the hepatitis, or more accurately the pericholangitis, is widespread throughout the liver, the site of any active obstruction would seem to be at the ampulla of Vater in order that the whole biliary system may be involved. Ivy,

in reviewing the physiology of the gall-bladder claims that there is a reciprocal functional relatishop in the choledocho-duodenal mechanism. The writer rather leans toward the idea that this relationship can be upset because of a poor functional integration of hereditary origin. If this were so, we have the basis of the stasis of the biliary system necessary to cause stone formation as outlined above. It would also account for those cases that have continued trouble even after cholecystectomy, for though the gall-bladder is removed still this hereditary mal-functioning is left; and of course the pericholangitis is undisturbed by operative procedure.

No attempt is made to correlate these findings with the clinical aspects of cholecystitis in this paper, but a few suggestions will serve to show that the problem is a live one, and well merits the attention of research and clinical workers alike. First it is evident that the gall-bladder should not be considered as a separate entity, but should only be considered in relation to the rest of the biliary tract. That is, we should speak of biliary system disease rather than cholangitis and cholecystitis. Secondly the possibility of some medical type of treatment may become feasible, when we are able to control the metabolism of the bile salts and cholesterol to such an extent that stones, which are present may be redissolved, as was accomplished in the case of the dog. There is also the interesting similarity between the formulae of cholesterol, the bile salts, the oestrogenic hormones, and the so-called carcinogenic substances. Lastly, there is the suggestion that a clinical study of the bile salts in the blood may prove of equal or even greater value than the Van den Bergh test. Some work has been done on this latter problem but it is too scanty to be of any practical importance at the present time.

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